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09/922,694	08/07/2001	Atsushi Suzuki	210377US0	8724

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EXAMINER	
UNDERDAHL, THANE E	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
05/13/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/922,694	SUZUKI ET AL.	
	Examiner	Art Unit	
	THANE UNDERDAHL	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-45,53-55,69 and 70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-45, 53-55, 69 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This Office Action is in response to the Applicant's reply received 2/18/09. Claims 40-45, 53-55, 69 and 70 are pending. No Claims are withdrawn. Claims 1-39 and 46-52 are cancelled. No Claims have been amended. No Claims are new. Claims 40-45, 53-55, 69 and 70 are considered in this Office Action.

Response to Applicant's Arguments— 35 U.S.C § 103

In the response submitted by the Applicant, the 35 U.S.C § 103 (a) rejection of claims 40, 41, 42, 69 and 70 over Saija et al., claims 40-45 and 69, 70 over Huang et al., claims 40, 41, 42, 53-55, 69 and 70 over Saija et al. in view of Yokozawa et al. and Manson et al. and Kitiyakara et al. were considered but not found persuasive.

The Applicant argues the unexpected results seen in the Table 1 pg 15 of the Specification at the one hour point clearly show that "co-administration of ferulic acid with caffeic acid and/or chlorogenic acid is clearly greater than the additive values of the individual administration of these compounds, thus providing evidence of synergism" (Applicant's Response, pg 3, bottom of page). However the Examiner cannot agree on this point. The Examiner has reproduce the values of Table 1, plots 1-3 below and showed the results of simple addition of the values and compared them to the actual values obtained. The following formula was used to sum the errors of the individual acids

$$\text{If } X = A + B \text{ or } X = A - B \text{, then: } \Delta X = \sqrt{\{(\Delta A)^2 + (\Delta B)^2\}}$$

This formula was used because the data is considered a simple combination of independent measurements.

Compound	Change in % ratio of Systolic Blood Pressure (all values obtained from Table 1)	Combinations of Acids	Calculated Values from Acids	Actual Values Obtained in Table 1 from the combining acids
Caffeic Acid (CA)	-10.2 ± 0.5	CA + FA	-9.5 ± 2.6	-11.3 ± 1.3
Chlorogenic Acid (CHA)	-7.2 ± 1.7	CHA + FA	-6.5 ± 3.1	-10.9 ± 0.8
Ferulic Acid (FA)	0.7 ± 2.6	CA + CHA + FA	-16.7 ± 3.1	-13.6 ± 3.4

It is clear that the calculated combinations of CA + FA and CA + CHA + FA are overlapping with the actual values when considering the errors. However the Examiner admits that the combination of CHA + FA does not. However the current claims read on anyone of these combinations. However since CA+FA and CA + CHA + FA do not show greater result than expected from simply adding the additional acids together the conclusion that they are synergistic is not convincing.

The Applicant argues that Examiner has overlooked the statistical significance reported in the table. However when reviewing the statistical date and how it was obtained (Applicant's Specification, pg 14) it is not clear how the existence of a "significant difference" is defined. Indeed it is unclear if the "significant difference" is based on the expected results of combining the acids or some other difference. The Examiner concedes that adding more compounds that perform the same function will indeed create a "significant difference" over a single compound alone, but that is not the

test for synergism, which require a greater than expected result for overcome obviousness (M.P.E.P. § 716.02(a) I).

Therefore the rejections stand and are repeated below.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40, 41, 42, 69 and 70 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Saija et al. (J Sci Food Agric, 1999).

These claims are to a composition consisting of :

a) Isolated or purified ferulic acid or an ester or pharmaceutically acceptable salt thereof, and

b) Isolated or purified caffeic acid and/or chlorogenic acid or pharmaceutically acceptable salts thereof, and

c) A suitable excipient or carrier

Wherein a) or b) are present in an amount sufficient to lower blood pressure or suppress a rise in blood pressure when administered to a mammal.

This composition can be prepared into various formulations including a tablet, pill, powder, drink, injection, or dermatological preparation. Claims 69 and 70 limit the mass of a) and b) in the composition. The Applicant is reminded that any limitation reciting intended uses for the compositions such as suppressing "a rise in blood

pressure in a mammal" (see claim 1) are given no patentable weight since the it is the components of the composition that are the point of novelty and not their use.

Saija et al. teach that both caffeic or ferulic acid can each be formed into compositions with phosphate buffer as a carrier and applied to the skin surface as a dermatological preparation (pg 477, col 2, 2nd full paragraph down). After the appropriate conversions from a 0.200 mL solution Saija et al. teach that ferulic acid is present at 0.14 mg and caffeic acid at 0.084 mg. While Saija et al. does not teach a composition comprising both caffeic and ferulic acid together this would be obvious to one of ordinary skill in the art since they teach both acids are useful for the exact same purpose. M.P.E.P. § 2144.06 states

> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."

Therefore it is *prima facie* obvious to one of ordinary skill in the art combine ferulic and caffeic acid in a single composition. Therefore this reference renders obvious claims 40, 41, 42, 69 and 70.

Claims 40-45 and 69, 70 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al.

Claims 43 and 44 limit the composition b) to a chlorogenic acid. Claim 44 limits the chlorogenic acid to a specific stereoisomer.

The descriptions of claims 40, 41, 42, 69 and 70 are recited in the previous 35 U.S.C § 103 rejection.

Huang et al. teach compositions comprising **TPA** (12-O-tetradecanoylphorbol-13-acetate) and either ferulic acid or caffeic acid or chlorogenic acid in a carrier of either acetone or acetone and DMSO (pg 5943, Table 1 and 2) and spread on the skin of mice (pg 5941, Abstract). The TPA is used as part of an assay to induce tumor formation and the ferulic, caffeic and chlorogenic acids are used to inhibit this TPA-induce tumor (pg 5941, Abstract). One of ordinary skill in the art would recognize that a pharmaceutical preparation of these acids would not have TPA and would consist only of the acid and carrier since inducing tumors would be counterproductive to therapy. Also since Huang et al. teach that chlorogenic acid, caffeic acid and ferulic acid are used for the same purpose it would be obvious to combine them into a composition consisting of all three. The support for this is found in M.P.E.P. § 2144.06, which states

> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."

Therefore it is *prima facie* obvious to one of ordinary skill in the art combine ferulic, chlorogenic and caffeic acid in a single composition in the absence of evidence of criticality or unexpected results.

Also with the appropriate conversions of the amounts of the acids in the solutions in Tables 1 of Huang et al. provides the following results:

Compound	MW (g/mol)	Amount (umol)	Grams
Chlorogenic acid	354.31	10	0.0035
		20	0.0071
Caffeic acid	180.16	10	0.0018
		20	0.0036
Ferulic acid	194.184	10	0.0019
		20	0.0039
		50	0.0097

While these mass values meet the limitations of claim 69 they do not meet the limitations of claim 70. However the volume of the sample was only 0.2 mL (see Text of Table 1). Since both claim 69 and 70 limit that absolute amount of the acids in solution and not the concentration, if the volume of the sample was increased through routine optimization by one of ordinary skill in the art to cover the surface area treated then mass of acids in the composition would meet the limitations of claim 70 (M.P.E.P. § 2144.05 II).

Therefore this reference renders obvious claims 40-45 and 69, 70.

Claims 40, 41, 42, 53-55, 69 and 70 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Saija et al. as applied to claim 40, 41, 42, 69 and 70 above,

and further in view of Yokozawa et al. and Manson et al. and Kitiyakara et al. (AEP, 1995).

The descriptions of claims 40, 41, 42, 69 and 70 are recited in the 35 U.S.C § 103 rejection over Saija et al. above and are applied here as well. Claims 53-55 are to a method that uses the composition of claim 40 to reduce hypertension.

While Saija et al. renders obvious the composition they do not teach that this composition is used to treat hypertension. Regardless this would be obvious to one of ordinary skill in the art in view of the teachings of Yokozawa et al. in view of those of Manson et al. and Kitiyakara et al. Saija et al. teach that both caffeic acid and ferulic acid are known antioxidants (Saija, Abstract). Yokozawa et al. teach that the antioxidant caffeic acid or its derivatives alone can reduce hypertension via a reduction in systolic and diastolic blood pressures (Yokozawa, Table 1). Manson et al. teach that dietary antioxidants in general reduce hypertension (Manson, pg 262, col 1, Antiatherogenic Effects of Antioxidant Vitamins). Indeed Kitiyakara et al. supports the teachings of Manson et al. by showing a wide range of antioxidants of varying size and structure and mechanisms are useful for treating hypertension (Kitiyakara, Table 1). Therefore one of ordinary skill in the art would think it obvious to apply the antioxidant composition of Saija et al. of caffeic and ferulic acid to treat hypertension in view of the art that shows antioxidants including caffeic acid alone are useful for such a purpose.

Therefore these references render obvious claims 40, 41, 42, 53-55, 69 and 70.

No claims are currently allowed in this application.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571)

272-9042. The examiner can normally be reached Monday through Thursday, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached at (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Thane Underdahl
Art Unit 1651

/Leon B Lankford/
Primary Examiner, Art Unit 1651